Early evidence of an emerging NPC treatment paradigm: adrabetadex use alongside arimoclomol and/or N-acetyl-L-leucine

Poster 6

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BACKGROUND

- Niemann-Pick disease type C (NPC) is a rare, progressive, neurodegenerative disorder caused by impaired cholesterol trafficking, resulting in cholesterol accumulation and downstream cellular dysfunction.[1]
- FDA-approved therapies for the neurological manifestations of NPC have distinct mechanisms of action, including arimoclomol (heat shock protein co-induction; approved in combination with miglustat (substrate reduction), for patients ≥2 years of age), and N-acetyl-L-leucine (NALL; modified amino acid therapy approved for patients with NPC weighing ≥15 kg).[2-4]
- Adrabetadex is an investigational intrathecal therapy for infantile-onset (I-NPC) and the only therapy designed to directly target accumulated intracellular cholesterol in the CNS, the central pathogenic driver of NPC, by restoring cholesterol trafficking.
- Adrabetadex remains the only therapy studied and shown to improve survival in both early and late I-NPC compared with matched external controls.[5]
- Because adrabetadex targets the central pathogenic driver of disease, complementary therapies with distinct mechanisms may be layered on top to address downstream manifestations or provide additive benefit.
- In a recent consensus publication, most experts completely or partially agreed that combination therapy should be considered for patients with confirmed NPC; however, limited data are available regarding initiation and use of combination therapy outside of miglustat.[4]
- This analysis represents the first systematic evaluation of treatment sequencing and combination therapy in NPC, characterizing the use of adrabetadex alongside arimoclomol and/or NALL in clinical practice.

OBJECTIVES

To describe baseline characteristics, treatment sequencing, and combination therapy patterns in a cohort of participants treated with adrabetadex plus arimoclomol and/or NALL in an adrabetadex expanded access program (EAP), and to explore evidence for an emerging treatment paradigm in NPC.

METHODS

- Individuals with infantile-, juvenile-, or adult-onset NPC were eligible to participate in an EAP for intrathecal adrabetadex.
- Enrollment in the EAP was initiated in 2013 and required that participants be ineligible for all currently enrolling clinical trials.
- The program permitted concomitant use of other NPC therapies, arimoclomol or NALL, after their approval, allowing evaluation of adrabetadex administered concomitantly with arimoclomol, NALL, or both.

RESULTS

- At the data cutoff of March 1, 2026, 33 participants had received adrabetadex with arimoclomol and/or NALL: 6 participants received adrabetadex with arimoclomol, 12 received adrabetadex with NALL, and 15 received adrabetadex, arimoclomol, and NALL (Table 1).
- All 33 participants received adrabetadex, while 27 (81.8%) received NALL, 21 (63.6%) arimoclomol, and 20 (60.6%) miglustat; 10 participants were exposed to all four therapies.
- Of these, 28 participants received adrabetadex through the EAP and then began treatment with arimoclomol and/or NALL following U.S. approval.
- A total of 5 participants (juvenile onset, n=3; late I-NPC, n=1; early I-NPC, n=1) received arimoclomol before U.S. approval and later added treatment with adrabetadex, following the approval of arimoclomol. These participants received arimoclomol for an average of 3.71 years before initiating treatment with adrabetadex.

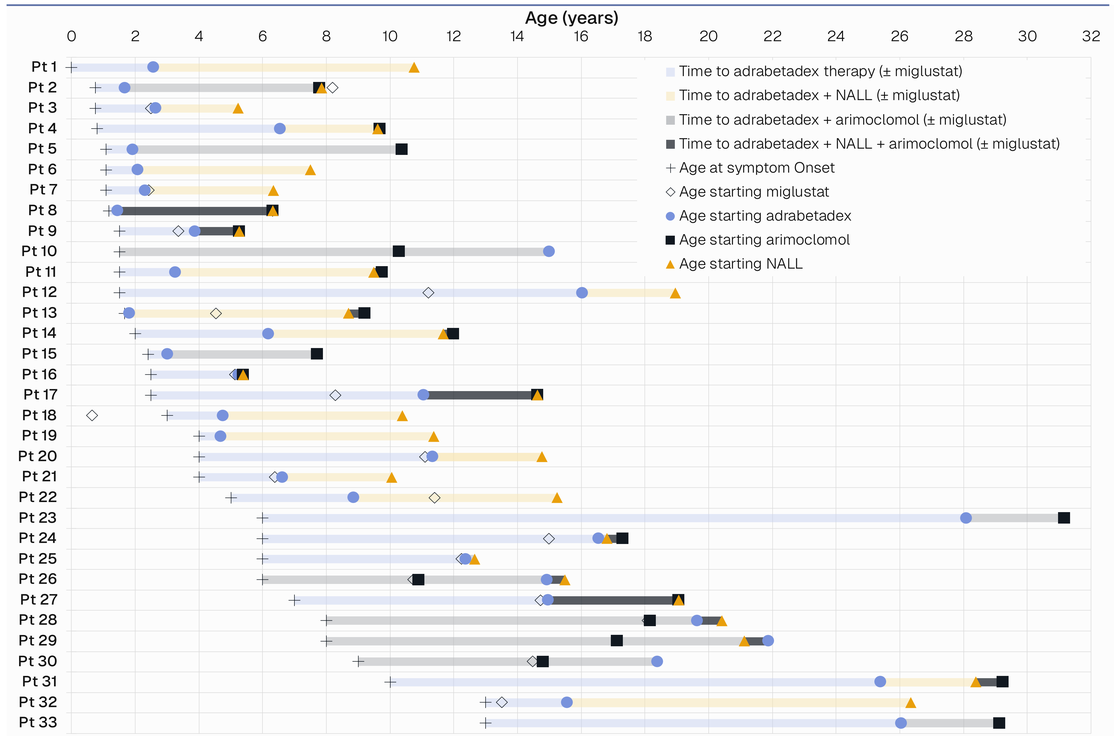
Table 1. Baseline Demographics and Disease Characteristics

	Adrabetadex + Arimoclomol (n=6)	Adrabetadex + NALL (n=12)	Adrabetadex + Arimoclomol + NALL (n=15)	ISS EAP Pool (N=85)
Age at neurological symptom onset category, n (%)				
<2 years old	2 (33.3)	5 (41.7)	6 (40.0)	26 (30.6)
2-6 years old	1 (16.7)	5 (41.7)	3 (20.0)	27 (31.8)
≥6 years old	3 (50.0)	2 (16.7)	6 (40.0)	31 (36.5)
Missing	0	0	0	1 (1.2)
Age at neurological symptom onset, years	n=6	n=12	n=15	N=84
Mean (SD)	5.5 (4.77)	3.6 (3.50)	4.0 (3.16)	5.8 (6.12)
Median (Q1, Q3)	4.2 (1.5, 9.0)	3.5 (1.1, 4.5)	2.5 (1.5, 7.0)	4.0 (1.5, 7.0)
Age at adrabetadex treatment start, years	n=6	n=12	n=15	N=84
Mean (SD)	15.2 (11.32)	6.8 (4.86)	9.8 (8.25)	11.8 (10.20)
Median (Q1, Q3)	16.7 (3.0, 26.0)	5.0 (2.0, 11.5)	6.0 (3.0, 16.0)	8.0 (3.0, 20.5)
Sex, n (%)				
Male	4 (66.7)	6 (50.0)	8 (53.3)	52 (61.2)
Female	2 (33.3)	6 (50.0)	7 (46.7)	32 (37.6)
Unknown	0	0	0	1 (1.2)
Race, n (%)				
Black or African American	0	0	0	1 (1.2)
White	6 (100.0)	11 (91.7)	14 (93.3)	74 (87.1)
Other	0	0	1 (6.7)	5 (5.9)
Multiple	0	1 (8.3)	0	1 (1.2)
Not Reported	0	0	0	4 (4.7)
Miglustat use at Baseline,[a] n (%)				
Yes	1 (16.7)	7 (58.3)	8 (53.3)	35 (41.2)
No	5 (83.3)	5 (41.7)	7 (46.7)	50 (58.8)
Miglustat initiation on or before start of arimoclomol and/or NALL,[a] n (%)				NA
Yes	1 (16.7)	9 (75.0)	9 (60.0)	
No	5 (83.3)	3 (25.0)	6 (40.0)	
Time from start of adrabetadex to initiation of arimoclomol and/or NALL, months	n=6	n=12	n=15	NA
Mean (SD)	22.0 (60.56)	59.8 (33.71)	27.9 (43.90)	
Median (Q1, Q3)	36.9 (-43.2, 56.3)	56.7 (38.1, 78.4)	36.8 (1.5, 65.8)	

[a]Miglustat use is derived from concomitant medications. Miglustat use was derived as Yes if there was a record of miglustat use in the concomitant medications at or prior to the first dose of study medication. Otherwise, Miglustat use is No. If miglustat was initiated at or before the start of arimoclomol and/or NALL, then 'Yes' otherwise 'No'.
Data analysis cutoff date is March 1, 2026. Percentages are based on the total number of participants in each treatment group (n). NA, not applicable; NALL, N-acetyl-l-leucine; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Early evidence of an emerging NPC treatment paradigm:

Figure 1. Timeline of Adrabetadex, Miglustat, Arimoclomol, and NALL Therapy for Individual Participants



- Of the 20 miglustat-treated participants, 15 had initiated miglustat prior to adrabetadex.
- Fifteen participants received adrabetadex, arimoclomol, and NALL. Of these, 12 participants initiated therapy with adrabetadex first and 3 initiated arimoclomol first. The sequence of therapy additions to adrabetadex in these 12 participants varied: 5 added arimoclomol and NALL simultaneously, 4 added NALL followed by arimoclomol, and 3 added arimoclomol followed by NALL.
- Thirty-two of the 33 patients remain active in the adrabetadex EAP.

CONCLUSIONS

- This analysis represents the first systematic evaluation of combination therapy use in NPC, characterizing treatment sequencing and use of adrabetadex alongside arimoclomol and/or NALL.
- Most participants initiated adrabetadex prior to complementary therapies, with arimoclomol and/or NALL frequently added after adrabetadex rather than used instead of adrabetadex.
- Importantly, >50% of participants evaluated had I-NPC, including >30% with early infantile disease, representing the youngest and most rapidly progressive patients, for whom approved treatment options remain limited or unavailable.
- These observations may help inform clinical decision-making regarding sequencing and use of therapies with complementary mechanisms of action in NPC, including infantile-onset disease.
- Observed treatment patterns may provide early evidence of an emerging treatment paradigm in which adrabetadex may serve as a foundational therapy while complementary therapies are layered based on patient need.

References

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